HERMES Time and Workflow Primary Paper

Statistical Analysis Plan

I. Study Aims

This is a post-hoc analysis of the pooled HERMES dataset, with the following specific aims:

A) To characterize the time period within which endovascular thrombectomy has been shown to confer benefit.
B) To delineate the extent to which treatment delay modifies the effect of endovascular reperfusion on functional outcomes, mortality, and intracranial hemorrhage
C) To characterize the length of discrete activity time intervals in the clinical workflow from symptom onset through endovascular reperfusion

II. General Analytic Approaches

Three general types of analyses of time effects will be made:

A) Time and Treatment-Arm Interaction: these analyses will use an ITT approach and compare the outcomes in the endovascular arm patients to the outcomes in the medical only arm patients.
B) Reperfusion Biologic and Clinical Effects: these analyses will be conducted in the subset of patients treated with endovascular intervention in whom substantial reperfusion (modified TICI 2b/3) was achieved.
C) Workflow: this analysis will delineate times of key interval steps of care, including all patients in both study arms up to randomization and endovascular arm patients only thereafter.

III. Descriptive Statistics

A) Results will be generated showing baseline variable distributions in the endovascular and the medical control arms, including all variables employed in any subsequent model. As appropriate, means (SD) and medians (IQR) for continuous variables and frequencies for categorical variables will be displayed.
B) Similarly, results will be generated showing baseline variable distributions by intervals for time from stroke onset to selection of treatment strategy (randomization) (OTRand).
C) A histogram will be generated for onset to treatment strategy time for all patients in the database, starting at 30 minutes with bin sizes of 30 minutes. Similar histograms will be generated starting at 60 minutes with bin sizes of 30 minutes for onset to arterial puncture and onset to reperfusion.

IV. Model Based Analysis

A) All model based analyses will use mixed methods modeling that takes into account between-trial variance by introducing two random effects variables, i.e., "trial" and trial*treatment."
B) Covariate adjustment for a prespecified set of baseline variables will be employed.

V. Recognition of Potential Effects of Imaging Selection for Patient Entry

A) Publications resulting from these analyses will note that, since imaging selection (ASPECTS thresholds, perfusion imaging, and collateral imaging) was used to some degree in many of the enrolled patients, time effects observed in this pooled population are likely less than those that would occur in a population in which no imaging-selection whatsoever was employed

VI. Time Interval Definitions

Time Interval Name	Time Interval Abbreviation	Definition
Onset to ED Door	OTD	Time from last known well to arrival at the ED of the study hospital
ED Door to Randomization	DTRand	Time from arrival at ED of study hospital to time of randomization
Onset to Randomization	OTRand	Time from last known well to time of randomization
Onset to Puncture	OTPunct	Time from last known well to time of arterial puncture (groin, radial, or carotid), among patients in the endovascular arm in whom arterial puncture was performed
Onset to Reperfusion	OTRep	Time from last known well to time of substantial reperfusion (TICI 2b or 3), among patients in the endovascular arm in whom substantial reperfusion was attained
ED Door to Reperfusion, Direct Arriving Patients	DTRep(direct)	Time from arrival at ED of study hospital to time of reperfusion, among endovascular arm patients who both arrived directly at the study hospital from the prehospital setting (no inter-hospital transfers) and achieved substantial reperfusion
Imaging to Reperfusion, Direct Arriving Patients	ITRep(direct)	Time from qualifying imaging to time of reperfusion, among endovascular arm patients who both arrived directly at the study hospital from the prehospital setting (no inter-hospital transfers) and achieved substantial reperfusion
Randomization to Puncture	RandTPunct	Time from randomization to time of arterial puncture (groin, radial, or carotid), among patients in the endovascular arm in whom arterial puncture was performed

Randomization to Reperfusion	RandTRep	Time from randomization to time of substantial reperfusion (TICI 2b or 3), among patients in the endovascular arm in whom substantial reperfusion was attained
Onset to Puncture (expected)	OTPunct(exp)	Time from last known well to expected arterial puncture time, should endovascular therapy be pursued, as available to the treating team at the time of the decision to pursue endovascular or medical treatment strategy. Calculated by adding to the OTRand value, for each patient in both the endovascular and medical groups, the study mean for RandTPunct of the trial in which they participated.
Onset to Reperfusion (expected)	OTRep(exp)	Time from last known well to expected reperfusion time, should endovascular therapy be pursued, as available to the treating team at the time of the decision to pursue endovascular or medical treatment strategy. Calculated by adding to the OTRand value, for each patient in both the endovascular and medical groups, the study mean for RandTRep of the trial in which they participated.
ED Door to Puncture (expected)	DTPunct(exp)	Time from arrival at ED of study hospital to expected arterial puncture time, should endovascular therapy be pursued, as available to the treating team at the time of the decision to pursue endovascular or medical treatment strategy. Calculated by adding to the DTRand value, for each patient in both the endovascular and medical groups, the study mean for RandTPunct of the trial in which they participated.
ED Door to Reperfusion (expected)	DTRep(exp)	Time from arrival at ED of study hospital to expected reperfusion time, should endovascular therapy be pursued, as available to the treating team at the time of the decision to pursue endovascular or medical treatment strategy. Calculated by adding to the DTRand value, for each patient in both the endovascular and medical groups,

		the study mean for RandTRep of the trial in which they participated.

VII. Comparisons of Treatment Arms

A.. Population analyzed

All comparisons of treatment arms will use an ITT approach and contrast the outcomes in the endovascular group to the outcomes in the medical control group.

B. Outcomes

1, Efficacy Outcomes

a. Primary: Degree of disability at 3 months (shift on the 7 level mRS across all ranks 0,1,2,3,4,5,6)
b. Secondary: Functional independence (mRS 0-2) at 3 months
c. Tertiary: Freedom from disability (mRS 0-1) at 3 months

2. Safety Outcomes

a. Primary: Death by 3 months
b. Secondary: Symptomatic intracerebral hemorrhage (using each study's definition) by 36h
c. Tertiary: Major radiologic parenchymal hematoma (PH2 hemorrhage within infarct field) by 36h

C. Analyses

C.1 Odds ratio analyses and graphs

Odds ratio analyses will model the dependence of the log odds of a particular outcome comparing endovascular treatment vs medical only control arm by time. Analyses of reduced disability (distribution of disability over the range of the mRS) will assess the common odds ratio using mixed methods ordinal logistic regression. Analyses of binary outcomes will assess odds ratios using mixed methods binary logistic regression. Covariate adjustment will be performed for the following six variables:

1. Age (linear variable)
2. Sex
3. Baseline stroke severity, as assessed by theNational Institutes of Health Stroke Scale (NIHSS) score (linear variable)
4. ASPECTS score at baseline
5. Clot location (3 level categorical variable - ICA, M1 MCA, M2 MCA)
6. Pretreatment with IV tPA (binary variable)

C.2 Treatment arm outcome comparison graphs

Graphs will be generated showing the relation of time vs outcome in the endovascular arm (point estimate line and 95% CI lines) and time vs outcome in the medical only control arm (point estimate line and 95% CI lines). Ordinal or binary logistic regression, as appropriate, will be used to model the dependence of the log odds of a particular outcome on the time interval being analyzed. Analyses will use the same covariates as in V.C.1.

C.3 Time intervals analyzed

1. OTRand
2. OTPunct(exp)

3. OTRep(exp)
4. OTRep(act/imp/imp)

Of these, OTPunct(exp) will be the lead analysis, as it reflects the time interval used in national treatment guideline recommendations.

C.4 Testing for time period within which evidence of benefit is present

For each efficacy outcome, odds ratio curves will be generated displaying the adjusted odds of better outcome with assignment to the endovascular arm compared with assignment to the medical arm, as a continuous function of change in the treatment time interval. The point estimate of the OR will be represented by a solid line and the 95% confidence intervals by dashed lines. The point at which the lower bound of the 95% CI crosses an OR 1.0 will be considered the outer limit of the time period within which data indicate benefit of therapy.

C.5 Testing for time – treatment arm interaction

The presence of a differential effect of time by randomized assignment will be evaluated in both binary and ordinal logistic regression models by testing the interaction term of time by randomized group for significance.

VIII. Reperfusion Analyses

A. Population analyzed

Reperfusion analyses will be conducted in endovascular arm patients treated with endovascular intervention in whom substantial reperfusion (mTICI 2b/3 post-procedure) was achieved.

A1. Subgroup analyses

Further subgroups of this population that will be analyzed are:

1. Intravenous thrombolysis with IV tPA prior to randomization
    a. IV tPA - treated
    b. IV tPA ineligible
    (All IV tPA eligible patients in the analyzed trials were treated with IV tPA.)
2. Target occlusion location subgroups [as read by the site]
    a. Intracranial internal carotid artery (ICA)
    b. M1 segment of the middle cerebral artery (MCA)
    c. M2 segment of the middle cerebral artery
3. Infarct degree at entry subgroups [as read by the site]
    a. ASPECTS 9-10
    b. ASPECTS 7-8
4. Age
    a. 18-79
    b. ≥ 80
5. Baseline stroke severity
    a. NIHSS 11-15
    b. NIHSS 16-20
    c. NIHSS > 20
6. Mode of arrival
    a. Direct to study hospital

b. Inter-hospital transfer from an outside, non-study hospital

B. Outcomes

- Reduced disability at 3 months (shift on the 7 level mRS across all ranks 0,1,2,3,4,5,6)
- Functional independence (mRS 0-2) at 3 months
- Alive and nondisabled (mRS 0-1) at 3 months
- Death by 3 months
- Symptomatic intracerebral hemorrhage (using each study's definition) by 36h
- Major radiologic parenchymal hematoma (PH2 hemorrhage within infarct field) by 36h

C. Time intervals analyzed

1. OTRand
2. OTPunct
3. OTRep
4. DTRep(direct)
5. ITRep(direct)

   Of these, OTRep will be the lead analysis, as it most closely reflects total ischemia time before reperfusion.

D. Analyses

1. Odds ratios

   Odds ratios by time will be generated using the endpoints and intervals indicated in VII.B and VII.C.
2. Magnitude of effect indices

   A) Binary analyses

      1. Benefit per hundred (BPH) = absolute risk reduction (ARR)
      2. Benefit per thousand (BPT) = BPH x 10
      3. Number needed to treat (NNT) = 100/ BPH
      4. Minutes needed to treat for 1 more patient to have better outcome (MNT) = Time interval in mins / BPH

   B) Ordinal analyses

      Outcome rates for all 7 mRS levels over time will be estimated using ordinal logistic regression, adjusting for the same covariates as in V.C.1. NNT values for improvement by 1 or more disability levels on the mRS will be derived from the differences in outcome rates yielded by the model at the earliest and latest time points with robust sample size (120 and 480 minutes for the onset to reperfusion model; 60 and 240 minutes for the door to reperfusion model). The BPT value over these intervals will be the mean of the BPT values calculated by the algorithmic joint outcome table method (Stroke 2009;40:2433-7) and the permutation test method (Stroke 2012;43:664-9). The BPT over 15 minutes for OTRep will be calculated by dividing the BPT over 360 minutes by 24 (360/15). The BPT over 15 minutes for

DTRep will be calculated by dividing the BPT over 180 minutes by 12 (180/15). From the BPT values, BPH, NNT, and MNT will be calculated as in VII.D.2.A above.

IX. Workflow Analyses

A. Time intervals to be analyzed

All Patients

- Onset to Emergency Department (ED) of the study hospital
- ED arrival to start of imaging (first brain image acquisition)
- Start of imaging to randomization
- ED arrival to IV tPA start (direct-arriving mode patients)
- Onset to IV tPA start
- ED arrival to randomization
- IV tPA start to randomization

All Endovascular Arm Patients

- Onset to arterial puncture
- ED arrival to arterial puncture
- Start of imaging to arterial puncture
- Randomization to arterial puncture

Endovascular Arm Patients with Substantial Reperfusion (mTICI 2b/3)

- Onset to substantial reperfusion
- ED arrival to substantial reperfusion
- Randomization to substantial reperfusion
- Arterial puncture to reperfusion

B. Analyses

Workflow time intervals will be reported using medians and interquartile ranges for each randomized group and by direct-arriving vs. inter-hospital transfer patients.

X. Power Considerations for Time – Treatment Interaction

A. Minimally clinically important difference (MCID)

The minimally clinically important difference to detect for decrement of benefit associated with treatment delay focused upon the efficacy differences in independent functional outcomes (mRS 0-2) that would occur due to delayed therapy. The scenarios being compared were ones in which endovascular therapy would be pursued in any case, differing only in whether it was pursued earlier or later. Financial costs associated with early versus later endovascular therapy were considered equivalent, as earlier or later endovascular intervention would both incur the same personnel and capital expenses. Safety outcomes, based on results of the pooled analysis, were considered neutral (SICH and PH2 hemorrhage rates did not differ with early versus late intervention) or supportive of earlier intervention (mortality was lower with earlier intervention).

The MCID for functional outcome was derived from 3 sources.

1. Survey of US stroke neurologists on delay of IV thrombolytic therapy

Findings were reviewed from a study in which a national survey was performed, obtaining responses from 103 US academic stroke neurologists.(Kaplan et al, Stroke 2015:46:AWP294) The study probed physician perception of the benefit-risk tradeoff involved in delaying start of IV tPA therapy in a noncompetent acute ischemic stroke patient in order to reach a legally authorized representative who could provide explicit informed consent. [The survey assessed the physician MCID for delaying therapy in order to maximize s the ethical value of beneficence (better outcomes) versus the the ethical value of autonomy (informed decision-making by patient/family).] Physicians were asked, among 1000 patients treated, how many patients experiencing worse outcomes would be acceptable in order to reach an informed consent provider. Over 90% of respondents indicated that no value higher than zero patients was acceptable for worse outcomes. This result indicates that, for the analogous reperfusion treatment of IV tPA, physicians consider the MCID for time delay to be 0 per 1000 patients.

2. Survey of US stroke neurologists on MCID for neuroprotective stroke therapy

   Findings were reviewed from a study in which a national survey was performed, obtaining responses from 122 US academic stroke neurologists.(Cranston et al, Stroke 2015;46:ATP73) The study was undertaken to characterize physician perception of the MCID to detect in clinical trials of neuroprotective stroke therapies, assuming the testing agent had no side effects. Physicians were asked, among 1000 patients treated, how many patients experiencing better outcomes would be needed in order to make the intervention worthwhile in use in ordinary clinical practice. The median (IQR) response was 13 (8 to > 20) patients per 1000 treated. Earlier versus later endovascular therapy is a similar decision, in that there is no incremental risk or cost associated with either earlier than later endovascular therapy or neuroprotective vs no neuroprotective therapy. The survey result accordingly suggests that physicians would consider the MCID for decrement in outcomes due to later start of endovascular therapy to be 13 per 1000 patients.

3. STEMI guidelines

   The closest analogy in another target organ to endovascular thrombectomy for acute ischemic stroke is percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI). Time-urgency in delivering PCI therapy is widely accepted as clinically important in treatment guidelines worldwide. Current recommendations are for door to balloon times of under 90 minutes, with general acceptance of the clinical relevance of shortening time intervals by as little as 15 minutes. A systematic analysis of 8 trials and registry studies, enrolling 15,827 patients, of the effect of PCI delay on outcome in STEMI found that delay for such an interval of 15 minutes is associated with worse outcomes (mortality) for 6 of every 1000 patients.(Aggarwal et al. Stroke 2016;47:A199)

Based on the above studies, the MCID for time delay in endovascular thrombectomy would lie in the range between a minimum of 0 and maximum of 13 per 1000 patients.

B. The power to detect treatment arm differences exceeding these MCIDs was assessed for the sample size of the current study and samples sizes 2-6 fold larger than the current study. In these simulations, the medical arm was assigned the mRS 0-2 outcome rate over time actually observed in the data; the endovascular arm was assigned mRS 0-2 outcome rates with 5, 10, and 20 per 1000 more independent outcomes associated with 1 hour faster therapy. The simulations determined the following power:

MCID	Multiple of Study Sample Size	N	Power
5 per 1000 patients treated 60m slower	Actual	1287	3%
	2-fold higher	2574	4%
	3-fold higher	3861	4%
	4-fold higher	5148	5%
	5-fold higher	6435	5%
	6-fold higher	7722	7%
10 per 1000 patients treated 60m slower	Actual	1287	7%
	2-fold higher	2574	8%
	3-fold higher	3861	9%
	4-fold higher	5148	11%
	5-fold higher	6435	13%
	6-fold higher	7722	15%
20 per 1000 patients treated 60m slower	Actual	1287	16%
	2-fold higher	2574	24%
	3-fold higher	3861	36%
	4-fold higher	5148	45%
	5-fold higher	6435	54%
	6-fold higher	7722	62%

X1. SAP Modification

This statistical analysis plan document provides detailed information on the final study methodology. It has been modified from an initial pre-analysis document to incorporate additional approaches undertaken to deepen understanding of initial findings. A formal protocol for the IPD analysis was not registered.